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Intellectual Property Law

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March 22, 2004

BY HAND DELIVERY
Shahnam J. Sharareh
Remsen Building
1600
Room 4C25

Re: U.S. Patent Serial No. 09/673,871
Inventor: Alexandre MARTI et al.
Our Ref: 12839/1

Dear Examiner Sharareh:

Further to your March 18, 2004 telephone conversations with Elizabeth Wieckowski, attached is a copy of each of the following documents which were submitted on March 19, 2004 by Express Mail to the Office of Petitions regarding the above-identified U.S. patent application:

(1) Petition Under §1.181
(2) an Amendment Under 37 C.F.R. §1.111;
(3) a Declaration Under 37 C.F.R. §1.132, including Exhibits A-I;
(4) a Transmittal Letter and Request for Extension of Time Pursuant to 37 C.F.R. § 1.136(a), which petitioned for a three-month extension of time from October 25, 2003 to Sunday, January 25, 2004;
(5) a Transmittal Letter for the Power of Attorney by Assignee of Entire Interest (Revocation of Prior Powers and Appointment of New Power);
(6) Power of Attorney by Assignee of Entire Interest (Revocation of Prior Powers Appointment of New Power);
(7) an original return receipt post card; and
(8) Exhibits 2-4.

If you require any additional documentation, please feel free to contact us.

Thank you for your attention to this matter.

Sincerely,
KENYON & KENYON

By: Lorraine Glorig
Lorraine A. Glorig,
Legal Assistant to Elizabeth M. Wieckowski

Enclosures

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER AND REQUEST FOR EXTENSION OF TIME PURSUANT TO 37 C.F.R. § 1.136(a)		Docket Number: 12839/1	
Application Number 09/673,817	Filing Date April 22, 1999	Examiner Shahnam J. Sharareh	Art Unit 1617
Invention Title SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES		Inventor(s) Alexandre MARTI et al.	

Address to:
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

1. Transmitted herewith for filing in the above identified patent application is an Amendment Under 37 C.F.R. § 1.111, together with a Declaration under 37 C.F.R. § 1.132, including Exhibits A-I.

2. Applicants respectfully request a three month extension of time in which to respond to the Office Action mailed July 25, 2003 for which a response period expiring on October 25, 2003 was set. The extended period expired on Sunday January 25, 2004. Therefore, a response is being timely filed on Monday January 26, 2004.

3. The Commissioner is hereby authorized to charge payment of the 37 C.F.R. § 1.136(a) extension fee of **$475.00** to the deposit account of **Kenyon & Kenyon**, deposit account number **11-0600**. The Commissioner is also authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 11-0600.

4. A duplicate copy of this form is enclosed.

Dated: January 26, 2004 By: Elizabeth M. Wieckowski

Elizabeth M. Wieckowski (Reg. No. 42,226)
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Express Mail No. EV 321 889 761US

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER		Docket Number: 12839/1	
Application Number 09/673,817	Filing Date April 22, 1999	Examiner Shahnam J. Sharareh	Art Unit 1617
Invention Title SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES		Inventor(s) Alexandre MARTI et al.	

Address to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing in the above identified patent application are Power of Attorney by Assignee of Entire Interest (Revocation of Prior Powers and Appointment of New Power).

Please record the Power and change of address in this application..

Dated: January 26, 2004 By: Elizabeth M. Wieckowski
Elizabeth M. Wieckowski (Reg. No. 42,226)

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EXPRESS MAIL NO. EV 321 889761US

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST (REVOCATION OF PRIOR POWERS AND APPOINTMENT OF NEW POWER)		Docket Number: 12839/1	
Application Number 09/673,817	Filing Date April 22, 1999	Examiner Shahnam J. Sharareh	Art Unit 1617
Invention Title SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES		Inventor(s) Alexandre MARTI et al.	

Address to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

As assignee of the entire interest of the above-identified application by virtue of an executed Assignment recorded in the U.S. Patent and Trademark Office on November 18, 2002, Reel 013494, Frame 0966, all powers of attorney previously given are hereby revoked and the following attorneys and/or agents are hereby appointed to prosecute and transact all business in the Patent and Trademark office connected therewith:

Donna M. Praiss (Reg. No. 34,232)
Richard L. DeLucia (Reg. No. 28,839)
Elizabeth M. Wieckowski (Reg. No. 42,226)

SEND CORRESPONDENCE, AND DIRECT TELEPHONE CALLS TO:

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Customer No. 26646
PATENT TRADEMARK OFFICE

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Date: Dec 12 2003

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Service des
Relations Industrielles
CM - Ecublens
CH-1015 LAUSANNE

By: _____

Name:

Title: G. Clerc
Head of SRI-EPFL

EV321889761US

EV321889761US

Case No. 6839/1 Atty. CNW

Ser. No. 09/673,817 Due Date 11/26/02

The Impressed Mail Room date stamp acknowledges receipt of the date indicated of:

- ☐ Application
- ☑ Amendment + Exhibits A-I
- ☐ Assignment
- ☐ Notice of Appeal
- ☐ Prior Art Statement
- ☐ Appeal Brief

DAP Rcvd 11-06-02

- ☑ Extension Request (3m)
- ☐ Priority Document
- ☐ Issue Fee
- ☑ ~~Declaration~~ POA
- ☐ Small Entity
- ☑ Declaration under 37 CFR 1.132

EV 321889761 US

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EV331889740US

Case No. 10839/1 Atty. ERW

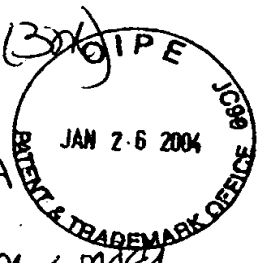
Ser. No. 09/673,817 Due Date 1/26/04

The Impressed Mail Room date stamp acknowledges receipt of the date indicated of:

- ☐ Application
- ☑ Amendment + Exhibits A-I
- ☐ Assignment
- ☐ Notice of Appeal
- ☐ Prior Art Statement
- ☐ Appeal Brief

DAP Accd 11-06-00

- ☑ Extension Request (3m) POA
- ☐ Priority Document
- ☐ Issue Fee
- ☑ ~~Declaration~~ POA
- ☐ Small Entity
- ☑ Declaration under 37 CFR 1.132



PATENT
12839/1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Alexandre MARTI et al.
Serial No.	:	09/673,~~817~~871
Filed	:	April 22, 1999
Title	:	SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES
Art Unit	:	1617
Examiner	:	S. J. Sharareh

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO JULY 25, 2003 OFFICE ACTION

SIR:

This Amendment is submitted in response to the Office Action mailed on July 25, 2003. A petition for a three-month extension of time from October 25, 2003 to January 25, 2004 is being concurrently submitted with authorization to charge the extension fee to deposit account no. 11-0600. Under 37 C.F.R. §1.7 when the day for taking any action or paying any fee in the U.S.P.T.O. falls on a Saturday, Sunday or on a Federal holiday within the District of Columbia, the action may be taken on the next succeeding business day which is not a Saturday, Sunday or on a Federal holiday. Accordingly, Applicants are timely submitting this amendment on Monday, January 26, 2004. Applicants respectfully request entry of the present Amendment in the above-identified case.

Please amend the above-identified application as follows:

Express Mail No. EV 321881761US

Amendments to the Specificati n

On page 3, please replace paragraph 8, which begins on line 25, with the following:

Said complementary substance may be an EDTA (ethylene diamine tetraacetate) ~~(tetra-acetate-diaminoethyl),~~ or ~~deferroxamine or desferal~~ deferoxamine mesylate (DESFERAL).

On page 4, please replace paragraph 3, which begins on line 13, with the following:

The solution can be completed by the addition of a complementary substance to prevent the PpIX ~~into form~~ from transforming into a heme by iron complexing in the living cells. This complementary substance may be an EDTA (ethylene diamine tetraacetate) ~~(tetra-acetate-diaminoethyl),~~ or ~~deferroxamine or desferal~~ deferoxamine mesylate (DESFERAL).

Amendments to the Claims

1-18. (Canceled)

19. (Currently Amended) A solution to be administered to a patient for at least one of diagnosis and treatment of tissue or a cell lesion by localized irradiation using a beam emitted by a source of light energy, comprising

a physiologically acceptable solvent; and

an ester of 5-aminolevulinic acid (E-ALA) for generating protoporphyrin IX (PpIX) which is present in the solution at a concentration of less than 1 % by weight.

20. (Currently Amended) The solution according to claim 19, wherein the concentration of the ester of 5-aminolevulinic acid (E-ALA) in the solution ranges between 0.01 % by weight to 0.5% by weight.

21. (Previously Added) The solution according to claim 19, wherein the ester of 5-aminolevulinic acid (E-ALA) is a hexylester of 5-aminolevulinic acid (h-ALA).

22. (Previously Amended) The solution according to claim 19, wherein the ester of 5-aminolevulinic acid (E-ALA) is dissolved in a solvent which is compatible with a human organism.

23. (Previously Added) The solution according to claim 22, wherein the solvent is selected from the group consisting of sterilized water, physiological NaCl solution, a phosphate buffer solution and alcohol.

24. (Previously Amended) The solution according to claim 22, wherein the solution contains a component to adjust the pH of the solution to a physiological value ranging from about 4.8 to about 8.1.

25. (Previously Added) The solution according to claim 19, wherein the solution comprises a complementary substance for preventing transformation of the protoporphyrin IX (PpIX) into a heme by iron complexing in the cells.

26. (Currently Amended) The solution according to claim 25, wherein the complementary substance is ~~diaminoethyl tetra acetate~~ ethylene diamine tetraacetate (EDTA).

27. (Currently Amended) The solution according to claim 25, wherein the complementary substance is ~~deferroxamine~~ deferoxamine mesylate.

28. (Canceled)

29. (Previously Amended) The solution according to claim 19, wherein the ester of 5-aminolevulinic acid (E-ALA) is dissolved in a solvent which is compatible with an animal organism.

30. (Previously Added) The solution according to claim 29, wherein the solvent is selected from the group consisting of sterilized water, physiological NaCl solution, a phosphate buffer solution and alcohol.

31. (Previously Amended) The solution according to claim 29, wherein the solution contains a component to adjust the pH of the solution to a physiological value ranging from about 4.8 to about 8.1.

32. (Currently Amended) The solution according to claim 19, wherein, following administering the ~~Solution~~ solution to the patient and irradiation of the tissue or the cell lesion by the source of light energy, a fluorescence emitted by protoporphyrin IX (PpIX) generated by the ester of 5-aminolevulinic acid (E-ALA) contained in the solution is detected to facilitate ~~diagnoses~~ diagnosis of the tissue or the cell lesion.

33. (Currently Amended) A solution to be administered to a patient for at least one of diagnosis and treatment of tissue or a cell lesion by localized irradiation using a beam emitted by a source of light energy, the solution comprising:

a physiologically acceptable solvent;

an ester of 5-aminolevulinic acid (E-ALA) for generating protoporphyrin IX (PpIX) which is dissolved in the solvent at a concentration of less than 1 % by weight;

a solution pH in the range of from about 4.8 to about 8.1; and

a complementary substance for preventing transformation of protoporphyrin IX (PpIX) into a heme by iron complexing in live cells, the

complementary substance selected from ~~diaminoethyl tetra acetate~~ ethylene diamine tetraacetate (EDTA), ~~deferroxamine~~ and ~~desferal~~ deferoxamine mesylate.

34. (Currently Amended) The solution according to claim 33, wherein the concentration of the ester of 5-aminolevulinic acid (E-ALA) in the solution ranges between 0.01 % by weight to 0.5% by weight.

35. (Currently Amended) The solution according to claim 34, wherein, following administering the solution to the patient and irradiation of the tissue or the cell lesion by the source of light energy, a fluorescence emitted by protoporphyrin IX (PpIX) generated by the ester of 5-aminolevulinic acid (E-ALA) contained in the solution is detected to facilitate ~~diagnoses~~ diagnosis of the tissue or the cell lesion.

REMARKS

Claims 19-35 are pending. Applicants have amended claims 19, 20, 26, 27, and 32-35, to correct punctuation and grammar; claims 27 and 33 have been amended to insert the generic name for DESFERAL; claims 26 and 33 have been amended to insert the correct the name for EDTA. These amendments are made to better clarify the scope of the present invention and not intended to narrow or limit the scope of the present invention. Claim 28 has been canceled without prejudice. The specification has been amended at pages 3 and 4 to insert the generic name for DESFERAL and to insert the correct the name for EDTA. No new matter has been added. Applicants respectfully request entry of the present amendment. Accordingly, claims 19-27 and 29-35 will be pending.

Objection to the Specification

The specification has been objected to for the use of the trademark Desferal, which should be capitalized and accompanied by its generic name.

In response, Applicants have amended the specification at pages 3 and 4 to recite "deferoxamine mesylate (DESFERAL)". Deferoxamine mesylate is the generic name for DESFERAL (*See*, PDR® Electronic Library™, 2003, page 1). Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the objection to the specification.

Claim Rejections under 35 U.S.C. § 112, second paragraph

Claims 27-28 and 33-35 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the recitation of "desferal", which is a trademark. Claim 28 has been rejected as being a duplicate of claim 27 since deferoxamine is the generic name for Desferal.

In response, applicants have amended claims 27 and 3 to recite "deferoxamine mesylate", the generic name for DESFERAL and to delete the trademark. Claim 28 has been canceled without prejudice. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27 and 33-35.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 19-35 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gierskcky et al. U.S. Patent No. 6,034,267 ("Gierskcky").

The Examiner states that Gierskcky teaches pharmaceutical compositions for treating or diagnosing a condition comprising an ester of Aminolevulanic acid (AIA) (sic). The Examiner states that Gierskcky teaches concentrations of the compounds of

about 1 to 50%, the use of chelating agents such as deferroxamine (sic), and methods of preparing and using ALA hexyl ester. The Examiner acknowledges that Gierskcky "fails to specifically use concentrations of ALA-esters in amounts of less than 1% and further specify the instant ranges of pH."

The Examiner asserts that "merely selecting proportions and ranges is not patentable absent a showing of criticality" (citations omitted), and that accordingly, in the absence of such a showing, it would have been *prima facie* obvious to optimize the concentration of Gierskcky's ALA-esters and their respective pH ranges because the ordinary artisan would have a reasonable expectation of success in achieving the desirable clinical outcome by modifying such values.

Applicants respectfully traverse the rejection and maintain that the pending claims are not *prima facie* obvious over Gierskcky.

In order to establish a *prima facie* case of obviousness, three criteria must be met: First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach all the claim limitations. (See, MPEP 2143) The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Initially, applicants note that Gierskcky is a U.S. national stage application under 35 U.S.C. §371 of PCT/GB96/00553, filed March 8, 1996, which published as WO96/28412 (hereinafter the "'412"). The '412 publication was previously cited against the subject application under 35 U.S.C. §102(b) and under 35 U.S.C. §103(a) in view of Chang et al. J. Photochem & Photobiol. 1997; 28 (2-3): 114-22; these rejections have been obviated by applicants March 10, 2003 amendment, which was entered upon the filing of a continued prosecution application on May 5, 2003. Since the Gierskcky disclosure is the same as the '412 publication and since the '412 publication does not render the present claims obvious for the reasons set forth in Applicants' aforementioned amendment, neither does Gierskcky.

Further, applicants note that no suggestion or motivation is provided by Gierskcky to modify the reference to arrive at the claimed invention. Moreover, as discussed below, no such suggestion or motivation is provided by the knowledge generally available to one of ordinary skill in the art to arrive at the claimed concentrations of ALA-esters below 1%. Neither does Gierskcky teach all the claim limitations, *i.e.*, ALA-ester doses lower than 1%.

Applicants submit that the claimed concentrations of ALA-esters provide unexpected results of producing higher amounts of protoporphyrin IX (PpIX) than 5-aminolevulinic acid (ALA) at much lower concentrations than ALA.

This conclusion is supported by the Declaration of Georges Wagnieres, Ph.D. under 37 C.F.R. §1.132, submitted herewith. Dr. Wagnieres is one of the co-inventors of the subject application. In the Declaration, Dr. Wagnieres describes the results of *in vitro* studies (paragraphs 10-12) and *in vivo* studies (paragraph 13). Comparative studies of administration of low doses of ALA-esters and high doses ALA were conducted, since high doses of ALA were used in photodynamic therapy at the time of the subject invention. Dr. Wagnieres also points out in paragraph 15 that at the time of the priority date of the subject application, in April 1998, the concentrations of ALA-esters studied were about two orders of magnitude higher than the concentrations of the present invention. Accordingly, one of skill in the art would have had no motivation to use the low doses of ALA-esters, and further, would have had no reasonable expectation of success in arriving at the claimed concentrations of the ALA-esters to achieve desired clinical results at that time of the invention. Therefore, neither Gierskcky nor the knowledge generally available to one of ordinary skill in the art at the time of the invention teach or suggest the claimed invention and the reasonable expectation of success thereof.

Since Gierskcky has not met the three criteria to establish a *prima facie* case of obviousness, the cited reference cannot render obvious the presently pending claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of presently pending claims 19-27 and 29-35 under 35 U.S.C. § 103.

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

Dated: January 26, 2004

By: Elizabeth M. Wieckowski

Elizabeth M. Wieckowski
Reg. No. 42,226

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(212) 425-7200

PATENT
12839/1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Alexandre MARTI et al.
Serial No.	:	09/673,817 71
Filed	:	April 22, 1999
Title	:	SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES
Art Unit	:	1617
Examiner	:	S. J. Sharareh

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

SIR:

I, GEORGES WAGNIÈRES, Ph. D., declare as follows:

1. I am a joint inventor of the subject matter of the above-identified application.

2. I received a doctorate degree from the Swiss Federal Institute of Technology (EPFL) in 1992. From July 1993 to August 1994, I was a postdoctoral fellow at the Harvard Medical School, Wellman Laboratories of Photomedicine, Boston Massachusetts.

3. I am currently an Adjoint scientifique (Project Leader) at the Swiss Federal Institute of Technology (EPFL) in Lausanne, Switzerland, and have served in this capacity since September 1994. From May 1992 to June 1993, I also served in the same capacity as I currently do at the EPFL.

4. In the past fourteen years, I have been a co-author of at least 69 papers published in peer-reviewed journals and have been an author or coauthor of 6 books, as well as over 60 other publications. Many of these publications are in the area of photodynamic therapy and diagnosis. (*See, e.g.*, F. Ludicke et al. "Photodynamic diagnosis of ovarian cancer using aminolevulinic acid hexylester: A preclinical study", Brit. J. of Cancer, 88(11), pp 1780-

1784, 2003; Radu A. et al. "Photodynamic therapy of early squamous cell cancers of the esophagus", Gastrointestinal Endoscopy Clin. North America, 10(3), pp 439-460, 2000).

5. I am a member of a number of professional societies, including the International Society for Optical Engineering, the Optical Society of America and the European Optical Society. I have served on the editorial board of a journal specializing in diagnostic optics, The Journal of Biomedical Optics, and have chaired numerous international conferences. Additional facts about my background and qualifications including a list of my publications are set forth in my *curriculum vitae*, attached as **Exhibit A**. An updated list of published articles is attached at the back of my *curriculum vitae*.

6. I have read and understand the outstanding Office Action mailed July 25, 2003 and the cited U.S. Patent No. 6,034,267 (hereinafter the "'267 patent"), issued on March 7, 2000 to Gierskcky et al.

7. The present application provides a solution for administration to a patient for diagnosis or treatment comprising a physiologically acceptable solvent and an ester of 5-aminolevulinic acid (E-ALA) which is present in the solution at a concentration of less than 1% by weight.

8. My co-inventors and I, and/or those working under our direction and supervision, performed experiments described in the application and obtained the results discussed therein. Below I provide additional details on these results, as well as subsequent studies.

9. Protoporphyrin IX ("PpIX"), a heme precursor, is used as a fluorescence marker and photosensitizing agent in photodynamic therapy. PpIX forms and accumulates in tissues with a high cellular turnover, *e.g.*, tumors. Therefore, an increase in intracellularly generated PpIX formation in response to exogenous stimulation by administration of 5-aminolevulinic acid (ALA) may be used for tumor destruction by photodynamic (PDT) therapy. ALA-mediated photodynamic therapy (PDT) was an emerging field for treatment of cancers since about 1989-1990. However, since ALA-mediated PDT is limited by ALA's poor ability to diffuse through cell membranes, solutions containing high doses of ALA of about 180 mM (about 3% w/w) have to be administered to increase PpIX production in the deep layers of cancerous lesions. Therefore, I have studied the comparative effects of administration ALA-esters and of ALA to determine optimal concentrations of these PpIX precursors for use in PDT and photodiagnosis.

10. In one study, two cell lines derived from human transitional cell carcinoma of the bladder, J82 and T24 cells, respectively, were incubated with ALA or esters of ALA, as described in P. Uehlinger et al. "5-Aminolevulinic acid and its derivatives: physical chemical properties and protoporphyrin IX formation in cultured cells", J. Photochem. Photobiol. B: Biol., 54, pp 72-80, 2000 (**Exhibit B**). The esters of ALA studied included ALA-methylester, ALA-ethylester, ALA-butylester, ALA-hexylester, and ALA-octylester.

11. In this study, I found that ALA-butylester, ALA-hexylester, and ALA-octylester not only produced PpIX formation at much lower concentrations than ALA, but also produced higher amounts of PpIX, as shown in the graphs for the J82 and T24 cells, respectively, which are adapted from Figure 3 of Uehlinger et al. 2000, and are attached as **Exhibit C**.

12. Experiments were also performed on bladder tissue *in vitro*, in which PpIX formation after administration of ALA or ALA-ethylester, ALA-butylester, ALA-hexylester, and ALA-octylester, were measured, as described in A. Marti et al. "Optimization of the Formation and Distribution of Protoporphyrin IX in the Urothelium: an In Vitro Approach", J. Urology, 162(2), pp 546-555, 1999, attached as **Exhibit D**. The results again demonstrated higher amounts of PpIX formation at much lower concentrations of ALA-ethylester, ALA-butylester, ALA-hexylester, and ALA-octylester than with ALA. These results are shown in **Exhibit E**, adapted from Figure 4 of Marti et al. 1999. A Table summarizing these results, attached as **Exhibit F**, shows the optimal concentrations of ALA and ALA esters for PpIX production. The Table (**Exhibit F**) indicates that the ALA-butylester, ALA-hexylester and ALA-octylester all achieved optimal PpIX levels at concentrations of less than 1%. The data in **Exhibits E** and **F** demonstrate that various concentrations below 1% of ALA-ethylester, ALA-butylester, ALA-hexylester, and ALA-octylester achieve high levels of PpIX formation.

13. *In vivo* clinical studies were performed to compare induction of PpIX with 8 mM of ALA-hexylester and 180 mM of ALA in a human pTa G2 cancer patient, as described in Lange et al. "Photodetection of early human bladder cancer based on the fluorescence of 5-aminolaevulinic acid hexylester-induced protoporphyrin IX: a pilot study, Br. J. Cancer, 80(1/2), pp 185-193, 1999 (**Exhibit G**). For ALA-HCl, 180 mM corresponds to 30.17 mg/ml or 3.02% (w/w), whereas 8 mM of ALA-hexylester HCl corresponds to 2 mg/ml or 0.2% (w/w). The results, derived from Lange et al, p. 190, last paragraph, are shown in **Exhibit H**. They demonstrate that higher levels of PpIX were formed with much lower concentrations of ALA-hexylester than ALA.

14. Prior to April 1998, other researchers studied the effects of concentrations of ALA-esters that were about two orders of magnitude higher than the concentrations of the present invention. For example, Peng et al. "Build-up of esterified aminolevulinic-acid-derivative-induced porphyrin fluorescence in normal mouse skin" J. Photochem. Photobiol B: 34 (1996):95-96 (**Exhibit I**), administered methylester, ethylester and propylester of ALA in a concentration of 150 mg/kg, *i.e.*, about 20% (w/w). Our studies, based on a mean patient weight of 75 kg, administered a dose of approximately 1.3 mg/kg, which is about two orders of magnitude lower than that used in Peng et al.

15. Therefore, it was unexpected by me that the lower doses of ALA-esters would produce higher levels of PpIX than the lowest doses of ALA-esters studied at the time of the present invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent or any reexamination certificate issued therefor.

Dated: 26th of JANUARY 2004

G. Wagnières

GEORGES WAGNIÈRES, Ph. D.

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER AND REQUEST FOR EXTENSION OF TIME PURSUANT TO 37 C.F.R. § 1.136(a)		Docket Number: 12839/1	
Application Number 09/673,817 71	Filing Date April 22, 1999	Examiner Shahnam J. Sharareh	Art Unit 1617
Invention Title SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES		Inventor(s) Alexandre MARTI et al.	

Address to:
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

1. Transmitted herewith for filing in the above identified patent application is an Amendment Under 37 C.F.R. § 1.111, together with a Declaration under 37 C.F.R. § 1.132, including Exhibits A-I.

2. Applicants respectfully request a three month extension of time in which to respond to the Office Action mailed July 25, 2003 for which a response period expiring on October 25, 2003 was set. The extended period expired on Sunday January 25, 2004. Therefore, a response is being timely filed on Monday January 26, 2004.

3. The Commissioner is hereby authorized to charge payment of the 37 C.F.R. § 1.136(a) extension fee of **$475.00** to the deposit account of **Kenyon & Kenyon**, deposit account number **11-0600**. The Commissioner is also authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 11-0600.

4. A duplicate copy of this form is enclosed.

Dated: January 26, 2004 By: Elizabeth M. Wieckowski

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U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER		Docket Number: 12839/1	
Application Number 09/673,847 71	Filing Date April 22, 1999	Examiner Shahnam J. Sharareh	Art Unit 1617
Invention Title SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES		Inventor(s) Alexandre MARTI et al.	

Address to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing in the above identified patent application are Power of Attorney by Assignee of Entire Interest (Revocation of Prior Powers and Appointment of New Power).

Please record the Power and change of address in this application..

Dated: January 26, 2004 By: Elizabeth M. Wieckowski
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U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST (REVOCATION OF PRIOR POWERS AND APPOINTMENT OF NEW POWER)		Docket Number: 12839/1	
Application Number 09/673,817 ~~817~~ 71	Filing Date April 22, 1999	Examiner Shahnam J. Sharareh	Art Unit 1617
Invention Title SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES		Inventor(s) Alexandre MARTI et al.	

Address to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

As assignee of the entire interest of the above-identified application by virtue of an executed Assignment recorded in the U.S. Patent and Trademark Office on November 18, 2002, Reel 013494, Frame 0966, all powers of attorney previously given are hereby revoked and the following attorneys and/or agents are hereby appointed to prosecute and transact all business in the Patent and Trademark office connected therewith:

Donna M. Praiss (Reg. No. 34,232)
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ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE. (EPFL)

Date: Dec 12 2003

EPFL - SRI
Service des
Relations Industrielles
CM - Ecublens
~~CH-1015 LAUSANNE~~

By: _____
Name:
Title: G. Clerc
Head of SRI-EPFL

EV321889761US

EV321889761US

Case No. 10839/171 Atty. ENW

Ser. No. 09/673,877 Due Date 11/26/04

The Impressed Mail Room date stamp acknowledges receipt of the date indicated of:

- ☐ Application
- ☑ Amendment + Exhibits A-I
- ☐ Assignment
- ☐ Notice of Appeal
- ☐ Prior Art Statement
- ☐ Appeal Brief

DAP ACCT 11-0600

- ☑ Extension Request (3mo)
- ☐ Priority Document
- ☐ Issue Fee
- ☑ ~~Declaration~~ POA
- ☐ Small Entity
- ☑ Declaration under 37 CFR 1.132